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EXAMINER	
BERTAGNA, ANGELA MARIE	

ART UNIT	PAPER NUMBER
1637	

DATE MAILED: 07/18/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/757,263	WANG, XIAO B.	
	Examiner	Art Unit	
	Angela Bertagna	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 May 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-48* is/are pending in the application.

4a) Of the above claim(s) *34-43* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-33 and 44-48* is/are rejected.

7)☒ Claim(s) *46* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *14 January 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 10/4/05, 1/4/05, 6/16/04, 6/14/04 (2 submissions), 6/7/04, 3/22/04, 2/5/04, 1/14/04
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election of Group I, claims 1-33 and 44-48 in the reply filed on May 25, 2006 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 34-43 withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on May 25, 2006.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Priority

Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120. The later-filed application must be an application for a patent for an invention that is also disclosed in the prior application (the parent or original non-provisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be

sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosures of the prior-filed applications, Application No. 09/862,417 (now USPN 6,824,980) and Provisional Application 60/209,987, fail to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. Specifically, the prior-filed applications do not provide support for hybridizing the equal-length extension products generated in the first hybridization reaction with a second primer and conducting a second primer extension reaction. Therefore, the examined claims (1-33 and 44-48) have not been granted benefit of the earlier filing date of the above applications (09/862,417 & 60/209,987), and the instant application filing date of January 14, 2004 has been used as the effective filing date.

Claim Objections

Claim 46 is objected to because of the following informalities: A period is missing at the end of the claim. Appropriate correction is required.

Claim Rejections - 35 USC § 112 (1st paragraph)

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 47 and 48 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter that was not described in

the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention

The claims are directed to methods of diagnosis based on detection of a primer extension product, generated in some cases from an oncogene. The invention is in a class of invention that the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The breadth of the claims

Claim 47 is broadly drawn to the diagnosis of an unspecified pathology based on the detection of an unspecified primer extension product. Since virtually every possible pathology

has some genetic-linked component, claim 47 encompasses diagnosis of nearly every pathological condition including, but not limited to, the disorders recited in paragraphs 50 and 58 of the specification: genetic disorders, cancer, heart disease, predisposition for a disease or syndrome, viral infection, bacterial infection, HIV, hepatitis, diabetes, autoimmune diseases, Li-Fraumeni Syndrome, Familial Retinoblastoma, Wilms Tumor, Neurofibromatosis Type 1, Neurofibromatosis Type 2, Familial Adenomatous Polyposis, Familial Breast Cancer (BRCA1 or BRCA 2), Multiple Endocrine Neoplasia Type 1, and Hereditary prostate cancer. These claims encompass diagnosis based on expression levels of an unspecified gene, diagnosis based on the presence of a variant polynucleotide, and even diagnosis based on the presence of any polynucleotide (wild-type or variant). In other words, claim 47 as recited, encompasses diagnosis of virtually *any* pathology based on detection of *any* primer extension product produced by the method of the invention. The range of diseases and conditions encompassed by claim 47 inherently possess radically different etiologies and symptoms and in many cases have no relationship to each other whatsoever. Also, detection based on expression level versus mutation is inherently different, subject to different controls, screening, etc. So the claims are extremely broad in scope, covering diagnosis of an immense number of diseases based on an immense variety of unspecified primer extension products, whereas the specification fails to positively diagnose even a single disease or condition based solely on the presence of a primer extension product produced by the method of the invention.

Quantity of Experimentation

The quantity of experimentation in this area is immense since there is complete variability as to whether or not the observation of a particular primer extension product in a sample obtained from a subject is sufficient to positively diagnose the subject. Regardless of whether the primer extension product represents a differentially expressed gene or a variant polynucleotide, significant study and experimentation including trials with dozens of patients would be required to determine that even a single disease is associated with any differentially expressed or variant gene or primer extension product generated therefrom. This would be an inventive, unpredictable and difficult undertaking in itself, and the efficacy of any of the genes, as a diagnostic for any particular disease would need to be demonstrated in a variety of patients with a statistically significant result. This would require years of inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

Wacholder et al (J. Natl. Cancer Institute (2004) 96(6): 434-442) notes that in studies of the association of mutations with specific diseases larger studies with 1500 participants have significantly more statistical power than smaller studies (see page 435). Similarly, Wei et al. (BMC Genomics (2004) 5: 87-96) teaches that the studies conducted using larger sample sizes with more replicates have much better statistical power and relevance compared to studies using small sample sizes with few replicates (see page 2, col. 1 and page 8). So, the quantity of experimentation factor supports the conclusion that a large quantity of experimentation, with the use of many hundreds, perhaps even thousands, of patient samples would be necessary to demonstrate an association for even one of genes (in differentially expressed or variant form)

disclosed by Applicant. To cover all possible disclosed differentially expressed and variant genes, tens of thousands of patient samples would be necessary, and to cover any fraction of the range of the disclosed diseases and conditions, hundreds of thousands of separate patients and the associated analyses would be required. This is a very large amount of experimentation.

The unpredictability of the art and the state of the prior art

The art teaches that it is entirely unpredictable how differentially expressed and variant genes are associated with disease. For example, Listgarten et al. (Clinical Cancer Research (2004) 10: 2725-2737) analyzed 98 single nucleotide polymorphisms (SNPs) distributed over 45 genes of potential relevance to breast cancer in 174 patients and compared the results with matched normal controls (see abstract). Listgarten concluded that "No single SNP site on its own could achieve more than 60% in predictive accuracy" (abstract) and encouraged detection of multiple SNPs to further improve accuracy (see abstract and also page 2735, last paragraph). Even with detection of multiple SNPs, though, Listgarten only report an increase in predictive accuracy to 69% (page 2726, col. 1). Finally, it is important to note that the studies of Listgarten were performed using patients whose breast cancer status was known. In other words, Listgarten demonstrated correlations between *some* SNPs (only 3 out of 98 tested) and a specific condition, breast cancer, but did not positively diagnose patients with unknown disease status based solely on the detection of variant polynucleotides.

Applicant's own work (Benoit et al. (2005) BioTechniques 38(4): 635-639) also illustrates the gap between detection of a differentially expressed or variant polynucleotide and a positive diagnosis. Benoit presents a colorimetric primer extension method of mutation

detection (see abstract). Benoit emphasizes that the detection of variant polynucleotides is useful to "detect early markers of disease or to *aid* in diagnosis (emphasis added)" (page 638, col. 1), but does not advocate diagnosis based solely on the detection of a variant polynucleotide. Furthermore, the teachings of Benoit further support the fact that not every variant is useful as a disease indicator. Benoit repeatedly suggests using the method to rapidly detect the best-studied (and likely the most reliable indicators) polynucleotide variants (page 638, for example).

Finally, the art is replete with evidence that gene association studies are typically wrong. In fact, Lucentini et al (The Scientist (2004) Vol 18) titled his article "Gene Association Studies Typically Wrong" and states "Two recent studies found that typically, when a finding is first published linking a given gene with a complex disease, there is only roughly a one-third chance that studies will reliably confirm the finding (see page 2 of printout)." This is consistent with the teaching of Wacholder et al (J. Natl. Cancer Institute (2004) 96(6): 434-442) who notes, "Too many reports of associations between genetic variants and common cancer sites and other complex diseases are false positives" (see abstract). Ioannidis (Nature genetics (2001) 29:306-309) further supports this conclusion in pointing out the heterogeneity of results among different studies of genetic polymorphisms (see abstract, for example). Finally, Wei et al. (BMC Genomics, 2004) states, "Microarray experiments are often performed with a small number of biological replicates, resulting in low statistical power for detecting differentially expressed genes and concomitant high false positive rates" (abstract).

Therefore, the art suggests that the detection of differentially expressed and/or variant genes is not usually sufficient for positive disease diagnosis, but rather must be combined with additional test results. The art also suggests that many reported associations between

differentially expressed and/or variant polynucleotides may be incorrect, thereby providing support for the conclusion that it is entirely unpredictable whether a given differentially expressed or variant gene will function in a diagnostic capacity for a given disease.

Working Examples

The specification has one relevant working example. Example 3 (page 23) teaches determination of the expression level of the cancer-related genes p53 and B-raf using the method of the invention. Two specific primer extension products were detected in relation to a specific disease (breast cancer). However, the RNA samples used in this example were isolated from human breast cancer tissue rather than an undiagnosed sample, and no indication is given, either in this example, or elsewhere in the specification that the method outlined in Example 3 can be used to positively diagnose cancer in the absence of additional tests.

Guidance in the Specification

The specification teaches generally that the expression level of oncogenes such as p53, growth factors, receptor tyrosine kinases, membrane-associated non-receptor tyrosine kinases, G-protein coupled receptors, membrane-associated G proteins, serine/threonine kinases, and nuclear DNA-binding/transcription factors may be used to diagnose cancer (paragraph 50). Paragraphs 51-57 teach specific cancers in which specific examples of the above oncogenes have been observed, but fails to teach that positive diagnosis is possible based solely on the presence of these nucleic acid sequences. Also, the specification is unclear as to what nucleic acid

sequence should be detected – the wild type or a variant form, and if a variant from is to be detected, which variant form.

Furthermore, the specification provides no guidance on methods or techniques to demonstrate an association between any specific disease and any specific mutation or gene. The specification even fails to provide any discussion or description of the scientific steps necessary to provide evidence that would associate a particular gene or variant thereof with a specific disorder from the extensive list of different types diseases and conditions.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

In the instant case, as discussed above, the level of unpredictability in the association of any differentially expressed or variant polynucleotide and any particular disease, where there is no teaching in the specification or art that any specific gene or gene variant is sufficient alone to diagnose any disease, in concert with the teaching that many published association studies are simply wrong supports a finding of undue experimentation. The specification provides the ordinary practitioner with no written description or guidance that leads to a reliable method of associating any specific differentially expressed or variant gene with any disease state. Furthermore, the specification does not provide guidance to overcome art recognized problems in the association of mutations and differentially expressed genes with diseases as shown by Lucentini, Wacholder, and Wei, among others. Finally, the quantity of experimentation is

immense. Thus, given the broad claims to the diagnosis of any pathology based on the detection of any primer extension product in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the absence of any working examples and the negative teachings in the prior art balanced only against the high skill level in the art, the inevitable conclusion is that it would require undue experimentation for one of skill in the art to perform the method of the claims as broadly written.

Claim Rejections - 35 USC § 112 (2nd paragraph)

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter that the applicant regards as his invention.

Claims 6, 9-11, and 24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "high stringency" in claim 6 is a relative term that renders the claim indefinite. The term "high stringency" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The specification only defines "high stringency" as "nucleic hybridization conditions, such as but not limited to a wash condition of 0.1X SSC, at 42°C" (page 18 of the specification). Since a wash at 42°C is not normally considered to be a high stringency wash, and given that high stringency conditions vary considerably depending on, for example, the sequences involved in the hybridization, the

ordinary practitioner would be unclear as to what constitutes a "high stringency" hybridization step according to the method of the invention.

Claim 9 recites the limitation "the labeled" in line 1. There is insufficient antecedent basis for this limitation in the claim. If this is the result of a typographical error ("the labeled" instead of "the label"), correction would easily overcome this rejection.

Claim 10 recites the limitation "the primer" in line 1. There is insufficient antecedent basis for this limitation in the claim, because since the independent claim 1 refers only to "a first primer" and "a second primer", it is unclear whether "the primer" refers to either or both of the first and second primers of claim 1.

Claim 11 recites the limitation "the nucleic acid of interest" in line 1. There is insufficient antecedent basis for this limitation in the claim, because since the independent claim 1 refers only to "a target polynucleotide". It is unclear whether there is another "nucleic acid of interest" besides the target polynucleotide of claim 1.

Claim 24 is indefinite, because the use of the phrase "moieties that allow immobilization of the second primer" causes the claim to be unclear as to whether or not the primers actually are linked to the solid support.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-33, 47, and 48 are rejected under 35 U.S.C. 102(b) as being anticipated by Koster et al. (US 2002/0042112 A1).

Regarding claim 1, Koster teaches a method (see Example 7, page 29-30) for detecting or quantifying a known target polynucleotide having a known nucleotide sequence comprising:

(a) hybridizing a first primer to the known target polynucleotide and extending the primer using a non-terminator nucleotide mixture formulated to produce equal length primer extension products (paragraph 395, where the PCR amplification inherently produces equal length primer extension products)

(b) hybridizing the equal length extension products to a second primer (paragraph 401)

(c) producing extension products from the second primer (paragraph 401)

(d) detecting the extension products from the second primer (paragraphs 404-405).

Regarding claim 2, the initial PCR conducted by Koster inherently generates products comprising a primer portion and an extended portion.

Regarding claim 3, the second primer of Koster hybridizes to the extended portion of the extension products of the first primer (compare, for example, the initial PCR primer sequences in paragraph 395 and the extension primer in paragraph 401, respectively).

Regarding claim 4, the second primer of Koster is not complementary to the first primer (compare, for example, the initial PCR primer sequences in paragraph 395 and the extension primer sequence in paragraph 401. These sequences are not complementary.).

Regarding claim 5, Koster teaches that the amount of detectable extension product correlates to the amount of target polynucleotide (paragraphs 407-408, where the MALDI signal correlates with the amount of target present).

Regarding claim 6, Koster teaches annealing of the first and second primers at 53°C and 50°C, respectively (paragraphs 395 & 401, respectively). These are high stringency hybridizations.

Regarding claim 7, Koster teaches that the extension products from the second primer are detected using mass spectroscopy (paragraphs 404-405).

Regarding claims 8 and 9, Koster teaches that the sequences of the extension products from the second primer were confirmed by Sanger sequencing (paragraph 408). Sanger sequencing inherently requires that the extension products comprise a detectable label, such as a fluorophore or a radioisotope.

Regarding claims 10 and 11, Koster teaches that the primers and target nucleic acid comprise DNA (see paragraphs 395 and 401 for the primer sequences and paragraph 393 teaches that the target is genomic DNA).

Regarding claims 12-14, Muller teaches enzymatic production of extension products (paragraphs 395 & 401). The template-dependent enzymes Taq DNA polymerase and Sequenase DNA polymerase were used to generate the extension products in the first and second extension reactions, respectively.

Regarding claims 15 and 22, Koster teaches enzymatic synthesis of the target nucleic acid in vitro (paragraph 395, where the target is PCR amplified).

Regarding claim 16, Koster teaches PCR of genomic DNA (paragraph 393).

Regarding claim 17, Muller teaches that the target polynucleotide comprises genomic DNA from an organism (paragraph 393).

Regarding claim 18, Koster teaches that genomic DNA may be isolated from organisms including plants, microorganisms, bacteria and viruses (paragraphs 18 & 197).

Regarding claims 19-21, Koster teaches isolation of DNA from human samples (paragraph 393).

Regarding claims 23 and 25, Koster teaches that the first primer comprises one or more moieties that permit affinity separation of the primer from unincorporated reagent and/or the polynucleotide of interest (paragraph 395 teaches that one of the initial PCR primers (SEQ ID No: 13) is biotinylated).

Regarding claim 24, as noted above, the language "the second primer comprises one or more moieties that allows immobilization" cause the claim to be indefinite as to whether the second primer is actually immobilized or is merely capable of being immobilized by any convenient means. Since the second primer of Koster is inherently capable of being immobilized, for example, via covalent coupling to a linker via the 5'terminus, the second primer of Koster "contains a moiety that allows immobilization", and therefore, anticipates the instant claim. Furthermore, Koster teaches immobilization of the second primer followed by extension (sequencing) of the hybridized target sequence (see paragraphs 230-231, for example).

Regarding claims 26 and 27, Koster teaches that the second primer is synthesized directly (via chemical synthesis) on a solid support to produce an immobilized second primer sequence (see paragraphs 319-320).

Regarding claim 28, Koster teaches that the second primer is immobilized onto a solid support to produce an immobilized target nucleic acid sequence (paragraphs 230-231).

Regarding claims 29 and 30, Koster teaches that the second primer can be cleaved from the solid support by a chemical process, specifically via cleavage of a photocleavable bond (paragraphs 231 and 234).

Regarding claim 31, Koster teaches that the solid support comprises beads, flat surfaces, chips, capillaries, pins, combs or wafers (paragraph 212).

Regarding claim 32, Koster teaches that the immobilization of the first primer is accomplished by hybridization between a complementary capture nucleic acid molecule, which has been previously immobilized to a solid support (paragraphs 220 and 230, for example).

Regarding claim 33, Koster teaches that immobilization is accomplished via direct bonding between the solid support and a portion of the nucleic acid molecule, which is distinct from the target nucleic acid sequence (paragraphs 229-233, esp. paragraph 233, where linkers are taught).

Regarding claim 47, Koster teaches a method comprising:

(a) obtaining from the host a sample comprising a polynucleotide (paragraph 395);

(b) contacting the sample with a first primer, the first primer comprising a nucleotide sequence complementary to a portion of a known target polynucleotide (paragraph 395);

(c) extending the primer using a non-terminator nucleotide mixture formulated to produce equal length primer extension products (paragraph 395, the PCR conducted by Koster inherently produces equal length extension products);

(d) hybridizing the equal length extension products to a second primer (paragraph 401);

(e) producing extension products from the second primer (paragraph 401); and

(f) detecting the extension products from the second primer (paragraph 404-405), where the detection of an extension product from the second primer is correlated with a pathology (paragraphs 407 and 409).

Regarding claim 48, Koster also teaches use of the method with oncogene target sequences (see for example, paragraphs 37-45).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 44-46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Koster et al. (US 2002/0042112 A1) in view of Wang (EP 1 162 278 A2; published December 12, 2001).

As discussed in greater detail above, Koster teaches a primer extension-based method of nucleic acid analysis.

Regarding claim 44, Koster teaches a method comprising:

(a) hybridizing a first primer to a target polynucleotide (paragraph 395)

(b) forming equal length primer extension products (paragraph 395)

(c) hybridizing a portion of the primer extension products to a second primer (paragraph 401)

(d) extending the second primer with at least one nucleotide having a detectable marker using a portion of the equal length extension products of (b) as a template (paragraph 401; the detectable label is the different ddNTP, detectable by mass spec)

(e) correlating the amount of detectable marker in the extension products of (d) with the amount of target polynucleotide (paragraphs 404-405; where detection by mass spec is an indication of the amount target present).

Koster teaches production of the equal length extension products using a mixture comprising all four dNTPs, rather than a mixure of three dNTPs.

Regarding claim 45, Koster teaches that the second primer hybridizes to the non-primer portion of the extension product (compare the initial primer sequences in paragraph 395 with the extension primer sequence in paragraph 401; the extension primer does not hybridize to the initial primer portion).

Regarding claim 46, Koster teaches that the extension primer may hybridize to the primer portion of the extension products of (b) (see Example 23, page 58, especially paragraphs 676 & 680, where the second primer (the PROBE primer in paragraph 680) hybridizes to the same sequence as the first primer (CKRΔ-F, SEQ ID No: 73, paragraph 676)).

Wang teaches an isometric primer extension assay for mutation detection. Briefly the method of Wang comprises: (a) annealing a primer to a target nucleic acid sequence of interest, (b) adding a mixture of chain-elongating and optionally terminator nucleotides, where at least one nucleotide of the four NTPs is either omitted or present only in chain-terminator form, (c) extending the primer, and (d) detecting primer extension product, and thereby detecting the nucleic acid of interest (see abstract and paragraph 8).

Regarding claim 44, Wang teaches mixtures of dNTPs useful for include (paragraph 10):

(a) dATP, dCTP, dGTP (2 different purines, 1 pyrimidine, all non-terminating)

(b) dATP, dCTP, dTTP or dUTP (2 different pyrimidines, 1 purine, all non-terminating)

(c) dATP, dGTP, dTTP or dUTP (2 different purines, 1 pyrimidine, all non-terminating)

(d) dCTP, dGTP, dTTP or dUTP (2 different pyrimidines, 1 purine, all non-terminating).

Wang specifically teaches that these mixtures are useful for generating equal length extension products, because since the target sequence is known and the omitted/terminator nucleotide is known, the exact length of the resulting extension products may be precisely predicted (see abstract and paragraphs 16-17).

It would have been prima facie obvious for one of ordinary skill in the art at the time of invention to utilize a nucleotide mixture taught by Wang in the primer extension method of Koster. Wang taught that the lack of a free nucleotide (obtained either by omitting the nucleotide or by using the chain-terminating form) reliably produced discrete length extension products (see paragraphs 16-17). Since Koster taught generation of the first extension products using a conventional PCR extension, where a long final extension step is included to maximize production of full-length (equal length) products, the ordinary practitioner would have been motivated to substitute the nucleotide mixtures taught by Wang, in order to obtain a more reliable method of generating equal length extension products without the need to rely on an additional extension step. Incorporation of the nucleotide mixtures of Wang into the method of Koster would have also provided the ordinary practitioner with an improved level of accuracy and reproducibility in the method, thereby providing further motivation to utilize these nucleotide mixtures to generate equal length extension products. Therefore, the ordinary

practitioner of the Koster method, interested in obtaining a faster, more reliable method of obtaining equal length extension products, would have been motivated to utilize the nucleotide mixtures taught by Wang, thus resulting in the instantly claimed methods.

Conclusion

No claims are currently allowable.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure: Braun et al. (Genomics (1997) 46: 18-13; cited in IDS), Braun et al. (Clinical Chemistry (1997) 43: 1151-1158; cited in IDS), Muller et al. (Human Molecular Genetics (2000) 9(5): 757-763; cited in IDS), and Fahy et al. (Nucleic Acids Research (1997) 25(15): 3102-3109; cited in IDS) teach the methods of detecting nucleic acids using two rounds of primer extension, according to claim 1.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Angela Bertagna whose telephone number is (571) 272-8291. The examiner can normally be reached on M-F 7:30-5 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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